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Cyclins in Meiosis: Lost in Translation

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In a recent issue of *Cell*, Carlile and Amon examine the regulation of four budding yeast B-type cyclins, crucial for regulating and distinguishing meoisis I and meoisis II divisions, and find a surprising diversity of behaviors and modes of regulation. In particular, Clb3 is regulated by a striking translational repression specific to meoisis I.

Meiosis is often portrayed as a specialized cell division, conjuring the image of a mitotic ("vegetative") division with bells and whistles. But when one looks in detail at what happens, and why and how, one is struck by the vast differences between the vegetative and the meiotic divisions. Many of the same proteins and processes are used, yes, but the relationships among them, and the regulatory wiring, are often unrecognizable.

In a vegetative division, chromosomes are replicated, and then at mitosis the paired sister chromatids segregate from each other, producing two identical cells. This process depends in part on the protein kinase activity of a cyclin-dependent kinase (CDK, Cdc28 in budding yeast) bound to and activated by a B-type cyclin (most importantly Clb2 in budding yeast). Entry into anaphase depends on high levels of CDK activity, and exit from anaphase depends on loss of this activity.

In a meiotic division (the point of which is to generate haploid gametes from a diploid parent), there is likewise replication of chromosomes, but followed by two rounds of division. At meoisis I, one pair of sister chromatids recombines with, then segregates from, its homologous pair (a division quite unlike anything seen in vegetative cells), while at meoisis II, the sister chromatids segregate from each other (a division similar to the vegetative division). For both meoisis I and meoisis II, entry into anaphase depends on high CDK protein kinase activity, and exit from anaphase depends on loss of this activity.

This complicated chromosome dance presents the cell with a number of challenges. First, chromosome behavior in meoisis I and meoisis II must be reliably different. Second, there is a need to coordinate loss of CDK activity to complete meoisis I with gain of CDK activity to initiate meoisis II. This second issue has been well-studied in *Xenopus* (e.g., Furuno et al., 1994; Hochegger et al., 2001).

Fortunately, budding yeast has six B-type cyclins, Clb1 through Clb6 (reviewed by Bloom and Cross, 2007). In principle, these could to some extent direct the Cdc28 cyclin-dependent kinase to phosphorylate different substrates, and furthermore, each cyclin could be independently regulated at various levels. In the vegetative cell cycle, some of these cyclins are regulated by transcription and by protein degradation, and the various cyclin-CDK complexes are differentially sensitive to inhibitors such as Sic1 and perhaps also to regulators such as Swe1 and Mih1 (reviewed by Bloom and Cross, 2007; Mendenhall and Hodge, 1998).

Thus, at least in principle, the differences between the vegetative, meoisis I, and meoisis II divisions could be partly due to differences in the properties and regulation of the six B-type cyclins. Indeed, genetic and other studies have shown that the major vegetative B-type cyclin, Clb2, is not expressed in meiosis (Grandin and Reed, 1993) and has no role in meiotic events. Loss of *CLB1*, *CLB3*, or *CLB4* has distinguishable meiotic phenotypes, though mechanistically it is not clear why (Dahmann and Futcher, 1995).

Carlile and Amon (2008) have addressed these issues by examining the behavior of the mRNAs, proteins, and protein kinase activities of Clb1, Clb3, Clb4, and Clb5 through meiosis. Key to this examination was a new method for producing highly synchronous meiotic cultures, allowing meoisis I and meoisis II to be resolved. They found a truly striking diversity in the patterns and modes of regulation of these related cyclin genes. For all four genes, transcription is upregulated before meoisis I and downregulated after meoisis II, and protein levels diminish with transcript levels, suggesting protein turnover. However, novel, gene-specific patterns of regulation by other mechanisms also appear. With respect

to Clb1, the most striking result is that its associated Cdc28 protein kinase activity is limited to meoisis I, even though transcript and protein continue to be present in meoisis II. Since none of the other cyclins loses associated kinase activity between meoisis I and II, this result implies the existence of a Clb1-specific kinase inhibitor. Clb4, similarly, displays a loss of associated protein kinase activity (but not loss of protein) part way through meoisis II. Clb5 is distinguished from its sibling cyclins by a loss of protein between meoisis I and meoisis II, despite the continued presence of mRNA, suggesting Clb5-specific protein degradation.

Finally, Clb3 showed a novel translational control. *CLB3* begins to be transcribed during meoisis I, but no Clb3 protein is seen until part way through meoisis II. Interfering with protein degradation using mutations or chemical inhibitors did not alter this finding, suggesting that regulated protein degradation was not involved. Instead, the 5′ untranslated region (UTR) of the *CLB3* transcript was required for this behavior: when *CLB3* was expressed in the context of a different 5′ UTR, protein was expressed in meoisis I, and when the *CLB3* 5′ UTR was transferred to another gene, the encoded protein was limited to meoisis II. It appears that the 5′ UTR of *CLB3* represses translation in meoisis I but not in meoisis II or in vegetative cells. The best-studied case of translational control in budding yeast involves the small open reading frames in the 5′ region of the *GCN4* transcript (Hinnebusch, 2005); there are no small open reading frames in the 5′ UTR of *CLB3*, so some distinct translational control mechanism must be involved. In principle, the same translational mechanism could coordinately regulate many other genes and in this way equip the meoisis II cell with a unique set of proteins.

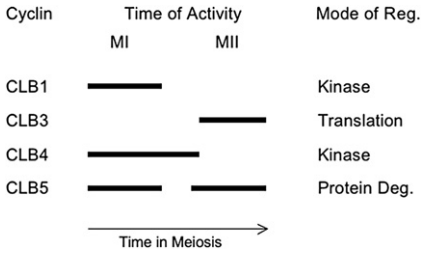

Figure 1. Timing of Cyclin Activity through Meiosis

Roughly speaking, then, Clb1, Clb4, and Clb5 are active during meoisis I, while Clb3 and Clb5 are active during meoisis II (Figure 1), with a hand-off from Clb4 to Clb3 occurring early in meoisis II. When Clb3 expression was forced in meoisis I using a heterologous promoter and 5′ UTR, a marked chromosome showed sister chomatid segregation (i.e., meoisis II segregation) in meoisis I. That is, forced expression in meoisis I of a cyclin that is usually restricted to meoisis II caused some chromosomes to segregate in a meoisis II pattern. However, forced expression of Clb2, a cyclin not usually expressed in meiosis at all, had a similar though smaller effect. It thus remains unclear whether the premature sister chromatid segregation is a qualitative effect (e.g., due to the particular substrate specificity mediated by Clb3 and Clb2) or a quantitative effect (an effect of excessive Clb activity, but of any kind).

Once again, we learn that cyclin regulation is almost bizarrely complex. However, one can begin to discern the yeast cell's strategy for the up-down-up-down regulation of CDK activity that must occur to give two consecutive chromosome divisions. After meoisis I, a (temporary) destabilization of Clb5 protein together with a specific inhibition of Clb1 kinase activity can drive CDK activity down, but relief of a block to the translation of preaccumulated Clb3 mRNA can quickly drive CDK activity back up again for meoisis II. The overall picture has some similarities to earlier findings in *Xenopus*; e.g., Hochegger et al., 2001, who found that meoisis I depends on cyclins B2 and B5, while meoisis II depends on cyclins B1 and B4, whose translation is activated after meoisis I. It is still unclear to what extent the differences between meoisis I and II are provoked by qualitative differences between Clb1 and Clb3, by quantitative differences in the amount of cyclin activity, or indeed by totally distinct regulators, perhaps including the translational regulator of Clb3. Finally, there appear to be as many as four novel mechanisms for regulating cyclin activity (though some may prove to be variants of known mechanisms), and it will be interesting to track these down.

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